

Psychedelic Effects of a Subanesthetic Concentration of Nitrous Oxide

Robert I. Block, PhD,* M. M. Ghoneim, MD,* Viney Kumar, MD,*
and Dharendra Pathak, MD*

*Department of Anesthesia, University of Iowa, Iowa City, IA USA

The subjective effects of nitrous oxide were examined by administering questionnaires to volunteers (16 men and 16 women) breathing 30% nitrous oxide or 100% oxygen. Nitrous oxide produced a variety of subjective effects, including some that are characteristic of psychedelic drugs, such as happy, euphoric mood changes, changes in body awareness and image, alterations of time perception, and experiences of a dreamy, detached reverie state. The subjective effects, including those of a psychedelic nature, were very similar to the subjective effects we observed in a previous study of nitrous oxide. However, euphoric mood changes were more pronounced, and adverse effects were less pronounced, in the present study, possibly due to the shorter duration of gas inhalation or the minimal tests of performance involved. Some other differences in subjective effects between the present and previous studies were identified by a discriminant analysis and seemed related to specific differences in experimental conditions. This suggests that the environment can influence which drug effects emerge, or at least their relative prominence. Clinicians should be familiar with the range of subjective effects that patients inhaling nitrous oxide may experience.

ffects, including some that are characteristic of psychedelic drugs.² Our results were consistent with an earlier study using a similar questionnaire³ and with the anecdotal descriptions of nineteenth century investigators such as William James.^{4,5}

Lysergic acid diethylamide (LSD) is the prototype of the psychedelic drugs. Other drugs that are generally classified as psychedelics include psilocybin, psilocin, dimethyltryptamine, diethyltryptamine, mescaline, and 2,5-dimethoxy-4-methylamphetamine.⁶ LSD and other psychedelics produce a multi-faceted pattern of subjective effects which is distinct from that of most other psychoactive drugs. Barber exhaustively reviewed the literature on subjective effects of LSD and classified these effects under categories such as changes in time perception, body image, and mood.⁷ In one of the most detailed investigations of subjective effects of LSD, Katz and colleagues developed a Subjective Drug Effects Questionnaire and administered it to subjects receiving LSD (50 μ g), amphetamine (15 mg), or placebo.⁸ A number of scales on the questionnaire showed subjective effects of LSD that differed from those of both amphetamine and placebo. In contrast, subjective effects of LSD resemble those of other psychedelics. For example, LSD, mescaline, and psilocybin are nearly indistinguishable in most subjective effects,⁷ as well as showing considerable cross-tolerance.⁶

It is frequently claimed that subjective effects of a psychedelic nature vary markedly depending on situational factors such as the setting in which a drug is administered.^{9,10} Barber, although indicating that little systematic research had been done, listed a number of factors generally believed to be important in influencing the subjective effects of LSD-type drugs, such as whether the drug is administered in a clinical or experimental setting, the types of activities required of the subject after drug administration, and whether the drug is administered to one subject or to a group.⁷ The belief in the importance of setting does not receive much support from the few systematic studies available, however. For example, with respect to marijuana, which produces some subjective effects of a psychedelic nature, it has been argued that many potential effects of the drug as typically used might not show up in the traditional "neutral" laboratory setting.⁹ Hollister and

Nitrous oxide in subanesthetic concentrations is widely used in dental and medical practice and is sometimes abused, presumably for its subjective effects.¹ In a previous study, we administered a questionnaire exploring the subjective effects of 30% nitrous oxide and found that the drug produced a variety of subjective ef-

Received April 11, 1989; accepted September 27, 1990.

Address correspondence to Robert I. Block, Ph.D., Department of Anesthesia, University of Iowa, Iowa City, IA 52242.

© 1990 by the American Dental Society of Anesthesiology

ISSN 0003-3006/90/\$3.50

colleagues examined this question, comparing effects of marijuana smoking in a neutral laboratory setting versus marijuana smoking in a private living room accompanied by pleasant visual, auditory, and other sensory stimulation.¹¹ Rated euphoria and scores on the hallucinogen and marijuana scales of the Addiction Research Center Inventory were sensitive to marijuana but not to environmental conditions. The authors concluded that, "The actual environment in which the drug is taken seems to play little, if any, role." Similarly, Atkinson and colleagues found that the subjective effects of 40% nitrous oxide were very similar in two studies, one involving administration in a small, plain laboratory room, with subjects lying supine, and the other involving administration in a larger, attractively decorated room with a homelike atmosphere, with subjects sitting in an upholstered recliner.³

In the present study, to investigate the consistency of the subjective effects of nitrous oxide under differing experimental conditions, we had subjects complete the same questionnaires assessing subjective drug effects and sedation that we used in our previous study.² The present and previous studies were very similar with respect to drug administration and the population from which subjects were drawn, but differed in test procedures, the previous study focusing on memory testing and the present one on measurement of skin conductance. We wanted to see if nitrous oxide produced a consistent pattern of subjective effects in the two studies and to see if any differences in subjective effects seemed related to differences in experimental conditions, which might provide some clues as to how setting modulates subjective effects.

METHODS

Thirty-two paid volunteers, 16 men and 16 women, were recruited by newspaper advertisements. They ranged from 18 to 30 years old (mean age 21.4 years). They were in good health according to a medical history questionnaire that they completed during a preliminary screening visit, during which they also provided information about drug use. Individuals were excluded if they were taking any medications which could influence the effects of nitrous oxide; if they had used three or more illicit drugs; or if they were heavy users of alcohol or marijuana. Subjects were individually tested. For 30 minutes, half the men and women inhaled 30% nitrous oxide and 70% oxygen. The remainder inhaled 100% oxygen, which seemed more appropriate as a control condition than room air since its oxygen content was closer to that of the experimental treatment. Subjects were assigned to treatments randomly. Testing was double-blind, i.e., neither the subjects nor the research assistants who administered the tests and scored the results knew which gas was

inhaled. Subjective ratings of drug effects, sedation, and anxiety were obtained after recovery from the acute effects, about 40 minutes after gas inhalation ceased. In the preceding skin conductance assessment, which took about 1.75 hours, skin conductance was measured while tape recordings of words and loud noises were played before, during, and after gas inhalation; then subjects' memory of the words was tested and they were asked to rate how unpleasant the loud noise had seemed. Further details concerning the subjects, design, drug treatment, and skin conductance assessment are available in a previous report concerning the skin conductance results.¹²

Sedation Ratings. Subjects rated their feelings on 11 scales. The ends of each of the seven-point scales (100 mm lines) were marked by adjectives representing the extremes of the dimension being rated. The adjective pairs, which are listed in the Appendix, predominantly reflected mental and physical sedation (e.g., Fuzzy vs. Clear-headed). The positive end of the scale appeared on the right side for five of the scales and on the left side for the other six scales. Subjects circled the number on each scale that best represented how they had felt during the 30 minutes of gas inhalation.

Drug Effect Ratings. Subjects then provided more detailed information about the subjective effects of gas inhalation. The questionnaire consisted of 68 brief descriptions of possible drug effects (e.g., "Have you felt more confused") from the Subjective Drug Effects Questionnaire⁸ plus 11 other descriptions written in a similar manner. For each description, subjects compared their experience during the 30 minutes of gas inhalation with the way they usually felt on a typical day and rated the extent to which the drug produced that effect on a seven-point scale (ranging from 1 = "No Drug Effect" to 7 = "Strong Drug Effect"). The questionnaire included 40 descriptions found to be "common" effects of nitrous oxide in the study by Atkinson and colleagues³ and 13 descriptions of adverse effects which were reported by one or more subjects in Atkinson's study. These descriptions are listed in the Appendix. The 40 descriptions of "common" effects included 29 classified by Atkinson into five categories of psychedelic drug effects derived from Barber⁷: changes in body awareness and image; alterations of time perception; experiences of a dreamy, detached reverie state; diminished cognitive-motor proficiency; and happy, euphoric mood changes.

Subjects were questioned further about their experiences and also provided information about anxiety by completing Spielberger's State-Trait Anxiety Inventory¹³ and a shortened version¹⁴ of Taylor's Manifest Anxiety Scale.¹⁵ These anxiety ratings were included to check that anxious individuals were proportionately represented in the nitrous oxide and oxygen groups, but were not intended or expected to show anxiolytic effects of nitrous

oxide, since subjects were not asked to rate their experience during the 30 minutes of gas inhalation.

Statistical Analyses. To determine the subjective effects of nitrous oxide, the Sedation and Drug Effect ratings were submitted to analyses of variance involving two between-subjects factors, drug group (nitrous oxide vs. oxygen) and sex. These analyses provided F tests for the overall effects of drug and sex and for the interaction of drug with sex. However, sex differences rarely influenced drug effects and will not be discussed. In addition, to compare the present results with those of our previous study, Pearson product-moment correlations and stepwise discriminant analysis were used.

RESULTS

Sedation Ratings. The mean ratings over all 11 items showed greater sedation in the nitrous oxide group than in the oxygen group, with means of 3.1 and 3.9, respectively, on a scale from 1 to 7, $F(1, 28) = 16.4$, $P < .001$. Seven of the individual items (64%) showed significant drug effects, all in the direction of greater sedation with nitrous oxide.

Drug Effect Ratings. The nitrous oxide group showed greater subjective effects than the oxygen group over all items and for the items reported as "common" effects of nitrous oxide by Atkinson,³ $F(1, 28) = 16.0$ and 31.8 , respectively, $P < .001$, but not for the "adverse" effects studied by Atkinson, $F(1, 28) < 1$. The mean ratings (on a scale from 1 to 7) for the nitrous oxide and oxygen groups were 3.0 and 2.0, respectively, for all items; 3.7 and 2.0 for the "common" items; and 1.6 and 1.6 for the adverse items. Twenty-nine (73%) of Atkinson's 40 "common" items, 3 (23%) of Atkinson's 13 adverse items, and 5 (19%) of the remaining 26 items showed significant drug effects, all but one in the direction of greater effects with nitrous oxide than oxygen. The exception was one of the "adverse" items, which did not actually indicate an adverse effect of nitrous oxide, since subjects breathing oxygen "felt sadder" than those breathing nitrous oxide.

Classifying items into categories of psychedelic drug effects following the method of Atkinson and of our previous study² indicated that nitrous oxide produced changes in body awareness and image, alterations of time perception, and experiences of a dreamy, detached reverie state; 11 (79%) of the 14 items in these categories showed significant effects. Nitrous oxide also produced happy, euphoric mood changes, with 9 (90%) of these 10 items showing significant effects. There was less evidence of diminished cognitive-motor proficiency, with 2 (40%) of these 5 items showing significant effects.

Correlational Analyses. Pearson product-moment cor-

relations were computed between the mean ratings of the nitrous oxide group for the individual Drug Effect and Sedation items and the corresponding mean ratings in our previous study.² These correlations were $r = 0.85$ ($N = 79$) for the Drug Effect items and $r = 0.74$ ($N = 11$) for the Sedation items, indicating that the present and previous studies showed substantial consistency in which items were rated high and which low.

Adjusted mean ratings for individual items in the present and previous studies were calculated, with the mean rating of the nitrous oxide group for each item in each study adjusted by subtracting the corresponding mean rating of the oxygen group. This adjustment controlled for placebo effects and for inherent differences among items unrelated to drugs. The correlation for the Drug Effect items was attenuated by this adjustment but remained high, $r = 0.62$ ($N = 79$). The correlation for the Sedation items was attenuated more substantially, $r = 0.42$ ($N = 11$), indicating that the individual items that were most sensitive to the sedative effects of nitrous oxide varied in the present and previous studies.

Discriminant Analysis. Although subjective effects of nitrous oxide in the present and previous studies were similar, some items showed differences. To explore whether these differences seemed related to differences in experimental conditions, the ratings of the subjects given nitrous oxide in the present and previous studies were compared in a stepwise discriminant analysis using a forward selection technique.¹⁶ Their ratings for each Drug Effect and Sedation item were adjusted by subtracting the corresponding mean rating under oxygen. At each step, the item entered in the model was the one that produced the most significant p value in an analysis of covariance comparing the ratings in the two studies, where the items already entered were covariates and the item under consideration was the dependent variable. The selection process ended when no unselected item produced a significance value of $P < .025$.

"Have you felt that your memory is worse?" entered first, "Have your hands or feet felt funny or strange?" entered second, and the Sedation rating for "Calm vs. Excited" entered third. No further items could be entered; for the three items, Wilks' $\lambda = 0.43$, $F(3, 28) = 12.1$, $P < .001$. Using these three items, 87.5% of the subjects could be correctly classified as to whether they had participated in the present or previous study.

Anxiety Ratings. The nitrous oxide and oxygen groups in the present study did not differ in their scores on the anxiety scales; no differences were expected since these scores did not assess anxiety during gas inhalation. The means for nitrous oxide and oxygen were 33.7 and 36.8, respectively, for Spielberger Trait anxiety; 31.1 and 33.2 for Spielberger State anxiety; and 4.4 and 5.6 for the Taylor Manifest Anxiety Scale.

DISCUSSION

The correlational analyses indicated that the subjective effects of nitrous oxide were very similar in the present and previous² studies. Nevertheless, some subjective effects differed in the two studies and the three items that were selected as the best discriminators in the discriminant analysis seemed plausibly related to differences in experimental conditions. Memory impairment was a prominent subjective effect of nitrous oxide in the previous study, in which subjects received numerous memory tests, but not in the present study, in which memory testing was a minor feature. Funny or strange feelings in the hands or feet were a prominent subjective effect in the present study, in which electrodes were attached to the subject's hand for measurement of skin conductance, but not in the previous study, which did not involve this procedure; the electrodes may have heightened subjects' attention to their hands. "Calm vs. Excited" ratings showed a treatment effect in the present study but not in the previous one, mainly because subjects receiving oxygen rated themselves as more excited in the present study than the previous one. This excitement could have been related to the loud (110 db SPL) noise that was presented as part of the skin conductance assessment in the present study. The maximal skin conductance responses elicited by the noise were larger for subjects who rated themselves as more excited, and these subjects also rated the noise as more unpleasant during gas inhalation ($r = 0.41$ in both cases). Nitrous oxide may have attenuated excitement from this source, since it reduced both the rated unpleasantness of the noise and the size of the skin conductance responses that it elicited.¹²

Given a drug like nitrous oxide with numerous potential subjective effects, the results of the discriminant analysis suggest that environmental conditions can influence which effects emerge, or at least their relative prominence. These results must be viewed as tentative, however. A large number of items were considered for selection and slightly different ratings could have caused other items, correlated with those that were selected, to be selected instead. In any case, these results should not obscure the general similarity of most subjective effects of nitrous oxide in the present and previous studies.

In both studies, nitrous oxide produced some subjective effects that are characteristic of psychedelic drugs, i.e., changes in body awareness and image, alterations of time perception, and experiences of a dreamy, detached reverie state. The present and previous studies also agreed with respect to diminished cognitive-motor proficiency; both found that the Drug Effect items were relatively insensitive to this effect, but simultaneously obtained evidence of diminished cognitive-motor proficiency in the Sedation ratings. The fifth category of psychedelic drug

effects provided the major difference in results between the studies; happy, euphoric mood changes were more pronounced in the present study, with 90% of these items showing significant drug effects, than in the previous one, where the corresponding figure was 50%. Another discrepancy between studies was consistent with this one. The Drug Effect ratings included 13 items pertaining to possible adverse effects of nitrous oxide examined by Atkinson.³ Nitrous oxide significantly increased mean ratings on these adverse items in our previous study, but not in the present one; and only two of the individual items showed significant adverse effects of nitrous oxide in the present study, compared to seven in the previous one. Since Atkinson also observed happy, euphoric mood changes and minimal adverse effects from nitrous oxide, we suggested in our previous study² that the more positive experiences of Atkinson's subjects relative to ours could have been related to various procedural differences including the higher concentration of nitrous oxide (40%), the shorter duration of gas inhalation (20 min), or the absence of performance tests in Atkinson's study. The present results are consistent with the latter two possibilities, since our present study resembled Atkinson's more closely than our previous one with respect to the duration of gas inhalation (30 vs. 99 minutes) and the minimal performance tests involved.

Overall, in the present study, 76% of the items in these five categories of psychedelic drug effects were influenced significantly by nitrous oxide, compared to only 30% of the remaining Drug Effect items. This preponderance of psychedelic effects was stronger in the present study than the previous study and provides further support for Atkinson's suggestion that nitrous oxide produces a moderate, incomplete psychedelic experience. This suggestion is also supported if one considers only items which were significant in both of our studies and which in this sense may be the most reliable effects of nitrous oxide; 48% of the psychedelic items but only 24% of the remaining items meet this criterion.

Subjects in the present study assessed the effects of nitrous oxide retrospectively, i.e., after recovery from these effects. We assumed that subjects would be able to remember and report subjective effects retrospectively with acceptable accuracy. This assumption seems plausible, but it would be interesting to test it systematically, by having subjects make repeated ratings of subjective effects, both during gas inhalation and retrospectively.

It would also be interesting to compare the subjective effects of nitrous oxide in patients undergoing dental surgery or other minor operations with those reported by our healthy volunteers. The minimal performance tests involved and the occurrence of an aversive stimulus (the loud noise) in the present study give it a slightly greater resemblance to the surgical setting than our previous

study. On the basis, patients might be predicted to report subjective effects more similar to those found in the present study than the previous one. But the “set” or expectations of patients with respect to drug effects might be different from volunteers and might influence their experience.

Since subanesthetic concentrations of nitrous oxide are commonly used in dental and medical practice, dentists and physicians should be familiar with the variety of subjective effects produced by the drug. These should be communicated to patients to alleviate possible anxiety and promote full compliance during administration.

ACKNOWLEDGEMENT

Thanks are due to Mrs. Kristen Rickey for assisting with the research.

APPENDIX

This Appendix lists the adjective pairs (*Sedation Ratings*) and descriptions (*Drug Effect Ratings*) used to assess subjective effects of nitrous oxide.

The *Sedation Ratings* were as follows: Alert/drowsy; calm/excited; fuzzy/clear-headed; well-coordinated/clumsy; mentally slow/quick-witted; lazy/energetic; incompetent/capable; attentive/dreamy; tense/relaxed; interested/bored; motivated/unmotivated.

The *Drug Effect Ratings* included 40 descriptions found to be “common” effects of nitrous oxide in a study by Atkinson and colleagues,³ including 29 classified by Atkinson into five categories of psychedelic drug effects, as follows:

Psychedelic Effects: (1) *Changes in body awareness and image:* Been noticing the way your body feels more than you usually do; arms or legs felt more numb; arms or legs felt tingling; hands or feet felt funny or strange; skin felt tingling; felt as if you are floating; body felt heavier; skin felt funny.

(2) *Alterations of time perception:* Been losing your sense of time; time seemed to be going faster.

(3) *Experiences of a dreamy, detached reverie state:* Had a weird feeling; imagination been more lively than usual; felt as if you were in a dream; things seemed more unreal than usual.

(4) *Diminished cognitive-motor proficiency:* Felt you have less control over your body; felt it's harder to talk; seemed harder than usual to describe in words how you feel; movements seemed slower; felt that you have less control over your thoughts.

(5) *Happy, euphoric mood changes:* Felt high; felt better than usual; felt less irritable; things seemed more pleas-

ing than usual; felt happier; felt more excited; felt extreme well-being; felt sillier; felt like laughing; felt as if you see the comical side of things more.

Other Common Effects: Felt not a care in the world; felt more free than usual; sounds seemed closer; body felt lighter; felt dizzy; lips felt more sensitive; eyesight been worse, more blurred than usual; felt as if you have less control over your feelings; been more aware of your skin; been noticing things around you less; thinking seemed clearer.

The *Drug Effect Ratings* also included 13 descriptions of adverse effects which were reported by one or more subjects in Atkinson's study, as follows: Felt afraid of losing control over your thoughts; felt afraid of losing control over your feelings; felt extreme anxiety; felt sick to your stomach (nauseous); felt worse than usual; felt more afraid; been afraid of losing control over your body; felt more irritable; head been aching; had a greater feeling of dislike for others; felt angrier; felt like crying; felt sadder.

REFERENCES

1. Rosenberg H, Orkin FK and Springstead J: Abuse of nitrous oxide. *Anesth Analg* 1979;58:104–106.
2. Block RI, Ghoneim MM, Hinrichs JV, Kumar V and Pathak D: Effects of a subanesthetic concentration of nitrous oxide on memory and subjective experience: Influence of assessment procedures and types of stimuli. *Human Psychopharmacology* 1988;3:257–265.
3. Atkinson RM, Morozumi P, Green JD and Kramer JC: Nitrous oxide intoxication: Subjective effects in healthy young men. *Journal of Psychedelic Drugs* 1977;9:317–328.
4. James W: II. On some Hegelisms. *Mind* 1882;7:186–208.
5. James W: Consciousness under nitrous oxide. *Psychol Rev* 1898;5:194–196.
6. Jaffe JH: Drug addiction and drug abuse. In: Gilman AG, Goodman LS, Rall TW, and Murad F, eds., *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Seventh Edition), New York, Macmillan Publishing Company, 1985; 532–581.
7. Barber TX: *LSD, Marijuana, Yoga, and Hypnosis*, Chicago, Aldine, 1970.
8. Katz MM, Waskow IE and Olsson J: Characterizing the psychological state produced by LSD. *J Abnorm Psychol* 1968;73:1–14.
9. Tart CT: Marijuana intoxication: Common experiences. *Nature* 1970;226:701–704.
10. Zinberg NE: On cannabis and health. *Journal of Psychedelic Drugs* 1979;11:135–144.
11. Hollister LE, Overall JE and Gerber ML: Marijuana and setting. *Arch Gen Psychiatry* 1975;32:798–801.
12. Block RI, Ghoneim MM, Fowles DC, Kumar V and Pathak D: Effects of a subanesthetic concentration of nitrous oxide on establishment, elicitation, and semantic and phonemic gener-

alization of classically conditioned skin conductance responses. *Pharmacol Biochem Behav* 1987;28:7–14.

13. Spielberger CD, Gorsuch RL and Lushene RE: *STAI Manual for the State-Trait Anxiety Inventory* (“Self-Evaluation Questionnaire”), Palo Alto, CA, Consulting Psychologists Press, 1970.

14. Bendig AW: The development of a short form of the Manifest Anxiety Scale. *J Consult Psychol* 1956;20:384.

15. Taylor JA: A personality scale of manifest anxiety. *J Abnorm Soc Psychol* 1953;48:285–290.

16. SAS Institute Inc.: *SAS User’s Guide: Statistics, Version 5 Edition*, Cary, NC, SAS Institute Inc., 1985 pp 749–762.